REMARKS/ARGUMENTS

Upon entry of the instant reply, claims 27, 28, 30-33 and 35-42 remain pending. Claims 27, 33, 39 and 42 are independent claims.

Reconsideration and allowance of the application are respectfully requested.

Response To Rejection Under 35 U.S.C. 112, first paragraph

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as the Examiner asserts that the specification, while being enabling for the treatment of Alzheimer's disease with a compound of formula (I) wherein R^5 is an optional substituted phenyl group (or C_6 aryl group), does not reasonably provide enablement for the treatment of Alzheimer's disease with a compound of formula (I) wherein R^5 is a hydrogen or optional subsittued alkyll, alkenyl, alkynyl or cycloalkyl group.

The rejection asserts that, on page 92-95 of the specification, *in vitro* assays showing several compounds with inhibitory activities on bovine cerebral TPK1 are presented. The rejection contends that there is no *in vivo* assay to show if the claimed compounds can increase memory, or inhibit neurodegeneration. The rejection contends that the inhibition of TPK1 only suppresses the Aβ neuortoxicity, which is asserted to not be conclusive on halting neurons from degeneration. The rejection concludes that Applicants' showing is insufficient to provide guidance on treating Alzheimer's disease using an array of compounds of formula (I).

The rejection points to Aldrich et al. (hereinafter "Aldrich"), U.S. Patent No. 6,107,301 as a showing of enablement for R^5 as a phenyl group, but contends that it would require undue experimentation to use compounds that are not analogous to those of Aldrich in the methods recited in claim 42.

In response, Applicants respectfully submit that one having ordinary skill in the art following the guidance in Applicants' specification would be able to practice the claimed invention without undue experimentation. One having ordinary skill in the art would understand, based upon Applicants' disclosure and/or knowledge available to one having ordinary skill, that the *in vitro* examples of suppression of Aβ neuortoxicity show enablement for treating Alzheimer's disease. As noted in Applicants' specification at page 93, beginning at line 11, "The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases."

Moreover, Applicants submit that their specification, at pages 1-3, provides detailed comments regarding abnormal accumulation and agglomeration of Aβ in Alzheimer disease. Accordingly, one having ordinary skill in the art would readily comprehend that tests relating to suppression of Aβ neuortoxicity provide enablement for the treatment of Alzheimer's disease.

In particular, and as discussed in Applicants' specification, beginning on page 1, with respect to Alzheimer disease it has known that the degree of appearance of two characteristic pathological changes of Alzheimer disease correlates well to the degree of intellectual dysfunction. It is disclosed that it has been shown, referencing Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985), that senile plaques accumulate extracellularly, and amyloid β has been elucidated as main components (abbreviated as "Aβ"). Moreover, it is disclosed that in the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF") accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component, referencing Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988).

Moreover, it is disclosed that, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ, referring to Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997). It is disclosed that from these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is disclosed that it is expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the

nerve cell death caused by ischemic cerebrovascular accidents, referring to Sai-shin Igaku [Latest Medicine], 49, 1506 (1994).

Still further, it is disclosed that it has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP") as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it is disclosed that it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders. It is also disclosed that other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, it is disclosed that as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

Still further, with respect to tau protein, it is disclosed that the tau protein is generally composed of a group of related proteins that forms several bands at

molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It is disclosed that it has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). Ii is also disclosed that an enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1"), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It is further disclosed that it has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993);

Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, Applicants respectfully submit that their disclosure enables the use of compounds which inhibit the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. Applicants submit that the recited method for therapeutic treatment of Alzheimer disease, which comprises administering to a patient a therapeutically effective amount of a substance selected from the group consisting of a pyrimidone compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof or a hydrate thereof is enabled.

The rejection merely utilizes the disclosure of one document, i.e., Aldrich, as providing enablement for R^5 as a phenyl group, and to attempt to establish, without any other suport, a lack of enablement of other compounds of Applicants' formula (I). The rejection does not show any consideration of the state of the art as set forth in Applicants' application. The question is whether Applicants have provided sufficient guidance so that one having ordinary skill in the art would be able to practice Applicants' invention without undue experimentation. Certainly, the answer to that question is in the affirmative, especially in view of the state of the art as discussed in Applicants' originally filed disclosure.

Applicants respectfully submit that the state of the art as discussed in the originally filed application is enabling for Applicants' claimed invention. Therefore, if this ground of rejection is maintained, the rejection must be supported by technical

reasoning with respect to the body of knowledge as disclosed by Applicants. In this regard, the Examiner is reminded that the burden is not on Applicants to establish that the claims are enabled, but is on the Examiner to support an enablement rejection using technical arguments. See, for example, "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph -- Enablement Chemical/Biotechnical Applications" and In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 369 (CCPA 1971).

In particular, it is noted that in Marzocchi, in reversing the rejection, the Court noted that the Patent Office should not be concerned with the breadth of the claims per se and that the burden of showing lack of enablement is on the Patent Office:

> Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicated nothing more than a concern over the breadth of the disputed term . . . . The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. . . .
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [lack of enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. at 369-70 (emphasis in original). Therefore, the burden of showing lack of enablement is on the Patent and Trademark Office.

In view of the above, Applicants respectfully submit that the claims are enabled, and the enablement rejection should be withdrawn.

Response To Art Based Rejections

The following rejections are set forth in the Office Action:

(a) Claims 27, 28, 30-33 and 35-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick et al. (hereinafter "Skulnick"), "Pyrimidinones. 1. 2-Amino-5-Halo-6-Aryl-4(3H)-Pyrimidinones. Interferon-Inducing Antiviral Agents", J. Med. Chem., Vol. 28, pp 1864-1869 (1985) in view of Spohr, U.S. Patent No. 6,096,753.

In this ground of rejection, it is asserted that Skulnick discloses two pyrimidinone compounds, i.e., compounds #112 and #113, that are asserted to be homologous to the compounds included in Applicants' claims with the following substituents:

i. R^2 is hydrogen or halogen atom

ii. R^3 is 4-pyridyl

iii. R^1 is $-N(R^4)-W-R^5$

iv. With W is a single bond and R^4 is a hydrogen, so that R^1 is reduced to $-NHR^5$.

The rejection notes a difference in the compounds by having NH_2 (or a primary amine) at the second position of the pyrimidine ring, and not $-NHR^5$ (or a secondary amine). The rejection further notes that Applicants argued that Skulnick does not provide motivation for modifying the second position of the pyrimidine ring, that is that Skulnick does not provide motivation for replacing $-NH_2$ with a secondary amine equivalent to $-NHR^5$ to maintain the same antiviral activity. However, the rejection asserts that such

deficiency in Skulnick can be overcome by the teaching of Spohr. In particular, the rejection is now utilizing Spohr to support modification of Skulnick by use of compounds of Spohr wherein R_1 represents Y, which can be $-NR_5R_{21}$; the disclosed R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, etc., and R_{21} can be hydrogen, alkyl, aryl, etc. The rejection contends that because Spohr's compounds can also treat viral infection, with the equivalent teaching provided, the skilled medicinal chemist would have been motivated to modify Skulnicks's compounds by replacing the $-NH_2$ with a secondary amine group to obtain compound of the instantly claimed formula (I) wherein R^1 is $-NHR^5$.

In response, Applicants respectfully once again submit that Skulnick is determining the effects of molecular modifications at the 6-position of the 2-amino-5-halo-4-pyrimidinone structure upon antiviral activity and IFN induction in mice. There is no motivation in Skulnick to modify the primary amine to a secondary amine. Moreover, there is no motivation to modify a secondary amine with various substitutions as recited in Applicants' claims.

The Examiner's attention is directed to Skulnick, page 1864, left-hand column, third paragraph, wherein it is disclosed that:

> Further biological evaluation of an initial lead candidate in this second-generation pyrimidinone series, 2-amino-5-bromo-6-phenyl-4(3H)-pyrimidinone (ABPP), served to unravel an intriguing spectrum. of immunomodulatory activity that may be related to its antiviral and antitumor activity. In efforts to elucidate the structure-activity relationship (SAR) profile of these bioactivities in this pyrimidinone series, we have systematically varied synthetically accessible points in the generic molecule. **We report herein the effects of molecular modifications at the 6-position of the 2-amino-5-halo-4-pyrimi-dinone structure upon antiviral activity (SFV and HSV-1) and IFN induction in mice.**

(Footnote omitted and emphasis added.)

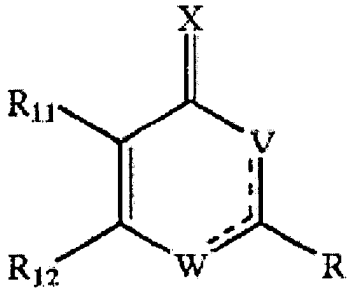
Thus, Skulnick discloses manipulation of the 6-position and does not teach or suggest the manipulation of the NH_2 group of the structure of the 2-amino-5-halo-4-pyrimidinoe structure disclosed therein. Moreover, Skulnick does not provide any teaching or suggestion as to why one having ordinary skill in the art would modify the NH_2 group from a primary amine to $-NHR^5$.

In an attempt to overcome the deficiencies of Skulnick, the rejection relies upon the disclosure of Spohr. However, one having ordinary skill in the art would not combine the disclosures of Skulnick and Spohr. Moreover, even if the sake of argument the disclosures were combined, the instantly claimed invention would not be at hand. Applicants submit that only teaching or suggestion to arrive at the compounds in Applicants' claims is in Applicants' specification, and a rejection cannot properly utilize Applicants' disclosure as the basis of a rejection.

Applicants submit that Spohr has a large disclosure of compounds, and one having

ordinary skill in the art would not pick and choose an alleged isolated disclosure of Spohr as asserted in the rejection to modify Skulnick. Spohr discloses a class of compounds useful in the prophylaxis and treatment of diseases, such as TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases and other maladies, such as pain and diabetes. In particular, the compounds of Spohr are disclosed as being useful for the prophylaxis and treatment of diseases or conditions involving inflammation. Spohr discloses that his invention also comprises pharmaceutical compositions comprising the compounds, methods for the prophylaxis and treatment of TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases, such as inflammatory, pain and diabetes diseases, using the compounds and compositions of his invention, and intermediates and processes useful for the preparation of the compounds of his invention. Spohr merely discloses at column 1, lines 39-41 that, "HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF-α." There does not appear to be an antiviral indication in such disclosure.

The compounds of Spohr's invention are disclosed to be represented by the following general structure:



wherein the dashed lines represent a double bond between C(R) and V or W (i.e., –V=C(R) – or –W=C(R)–) and V, W, X, R, R^{11} and R^{12} are as defined in the patent.

A review of the whole disclosure of Spohr reveals that there is diverse disclosure therein without any motivation for modifying Skulnick in the manner asserted in the rejection of record. This is especially the case where Skulnick appears to be determining the effects of molecular modifications at the 6-position of the 2-amino-5-halo-4-pyrimidinone structure upon antiviral activity and IFN induction in mice as compared to the utilities disclosed by Spohr, such as anti-inflammatory properties.

The Examiner's attention is once again directed to *In re Grabiak*, 226 USPQ 870 (CAFC 1985) wherein the court stated that, "None of these cases requires the result that a thioester derivative may be deemed *prima facie* obvious from the corresponding ester in the absence of prior art on this point." In the instant situation, there is nothing in the prior

art that teaches or suggests any type of substitution in Skulnick that would arrive at Applicants' claims.

Accordingly, this ground of rejection should be withdrawn.

(b) Claims 27, 28, 30-33 and 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aldrich, U.S. Patent No. 6,107,301.

In this ground of rejection, an intermediate in a process of producing compound XVI at column 36 of Aldrich and first paragraph of column 37 is referenced, and it is contended that the final product can include such compounds as well.

In response, Applicants note that this portion of Aldrich discloses compounds of Formula (I) wherein J, K, and L are CH and Z is C^2 and V and Y are N can also be prepared by the route outlined in Scheme 4. Aldrich discloses that the guanidinium salt (XII) was reacted with a β-ketoester (XV) in the presence of a base such as an alkoxide in the corresponding alcoholic solvent to give the adduct (XVI). Aldrich further discloses treatment of the hydroxy group in (XVI) with either phosphorous oxychloride, phosphorous oxybromide, methanesulfonyl chloride, p-toluenesulfonyl chloride, or trifluoromethanesulfonic anhydride provided (XVII), wherein the L is a leaving group and is, respectively, Cl, Br, I, OMs, OTs, or OTf. The L group of (XVII) is disclosed as being displaced with a nucleophile such as NR^6 R^7, OR^6, SR^6, CN, an organolithium, organomagnesium, organosodium, organopotassium, an alkyl cuprate, or in general an organometallic reagent to the corresponding adduct (IX), which is disclosed as being further alkylated under the standard conditions to produce (XVIII).

Applicants submit that intermediates as disclosed in Aldrich do not provide any motivation for arriving at Applicants' compounds, especially when there is no motivation to stop the process for synthesizing the disclosed end product and isolating the claimed intermediate. In this regard, the Examiner's attention is directed to *In re Stemniski*, 170 USPQ 343 (CCPA 1971) and *In re Lalu and Foulletier*, 223 USPQ 1257 (CAFC 1984).

Applicants respectfully submit that Aldrich does not appear to disclose any utility for the intermediates except as intermediates. There is no motivation in Aldrich to stop the disclosed synthesis and investigate properties of the intermediate with any expectation of success as to any properties for other compounds disclosed in Aldrich.

Accordingly, the rejection of record should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wishes to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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